Treatment of bone diseases with bisphosphonates, excluding osteoporosis

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The main biologic action of bisphosphonates consists of the inhibition of osteoclastic bone resorption, and, at least, for the drugs introduced after etidronate, without any significant inhibition of bone mineralization. Bisphosphonates therefore play a major role in conditions that are characterized, at least partly, by an increased bone resorption. Primary and secondary osteoporosis by far constitute the most widespread indications for bisphosphonates, mostly because recent published trials have demonstrated their ability to prevent fractures. Potentially crippling conditions such as symptomatic Paget disease of bone remain a major therapeutic challenge for bisphosphonates, but the prevention of the major complications such as sarcoma has still to be proven. The availability of more potent bisphosphonates, less toxic for bones, has certainly widened the therapeutic interventions to asymptomatic patients, bearing in mind the various potential troublesome complications. Fibrous dysplasia resembles, in certain aspects, Paget disease; it is therefore not surprising that bisphosphonate therapy has been proposed in this indication. With the aging of world populations, more and more cancers will be diagnosed. For those with a bone metastatic propensity or malignant hematologic condition, such as multiple myeloma, the most recent generation of more potent bisphosphonates may bring more comfort to crippled patients and even, hopefully, have a direct antitumoral activity, if used synergistically with the armamentarium already available to the clinician. New indications for bisphosphonates include osteogenesis imperfecta both in children and adults. In the future, they might be used in the prevention of erosions in rheumatoid arthritis and of loosening of joint prostheses, as well as possibly in osteoarthritis. Now that the fear of theoretically freezing bone remodeling has been reasonably dismissed, potential uses for bisphosphonates might be considered nearly infinite. Curr Opin Rheumatol 2000, 12:331–335

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Abbreviation

BMD bone mineral density

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The bisphosphonates are synthetic compounds whose main biologic action consists in inhibiting osteoclastic bone resorption. They are, therefore, used increasingly in the treatment of osteoporosis, which constitutes a major burden for Western societies through the dramatic increase in the incidence of fractures.

Bisphosphonates also have a major role in other conditions that involve increased bone resorption, notably Paget disease of bone, hypercalcemia of malignancy, multiple myeloma, and bone metastases, especially in breast cancer. New potential indications are osteogenesis imperfecta in children and adults, and in the future these agents could be used for the prevention of loosening of joint prostheses, the reduction of bone loss associated with periodontal disease, and the prevention of erosions in rheumatoid arthritis. Further applications could also be developed in the treatment of other joint diseases, such as osteoarthritis. Furthermore, for the most potent bisphosphonates, extended use in cancers can be envisaged in order to take advantage of their potential antitumor efficacy and to diminish the morbidity and improve the survival.

Mechanisms of action

The selectivity of bisphosphonates for bone rather than for other tissues was the origin of their wide use in clinical practice. Given the fact that they are analogues of inorganic pyrophosphate, it seems likely that bisphosphonates when internalized by osteoclasts interfere with one or several of the numerous biochemical intracellular pathways that involve pyrophosphate compounds and that are required for normal cell function. Recent mechanistic studies show that bisphosphonates can be classified into at least two groups with different modes of action [1•]. The bisphosphonates that most closely resemble pyrophosphate (*eg*, the first-generation bisphosphonates clodronate and etidronate) can be incorporated into cytotoxic adenosine triphosphate (ATP) analogues, whereas more potent nitrogen-containing bisphosphonates interfere with other reactions (*eg*, in the mevalonate pathway) and may affect cellular activity such as apoptosis by interfering with protein prenylation, and, therefore, the intracellular trafficking of key regulatory proteins [1•,2]. Recent findings suggest that bisphosphonates act directly on the osteoclast to induce apoptosis and that caspase cleavage of mammalian sterile 20-like kinase 1 is part of the apoptotic pathway [2]. In another recent paper, it has been hypothesized that alendronate, acting directly on osteoclasts, inhibits a rate-limiting step in the cholesterol biosynthesis pathway, essential for osteoclast function [3]. This inhibition is prevented by exogenous geranylgeraniol, probably required for prenylation of GTP-binding proteins that control cytoskeletal reorganization, vesicular fusion, and apoptosis, processes involved in osteoclast activation and survival [4].

Paget disease of bone

Among the conditions with high bone turnover, Paget disease involves one of the highest rates of bone remodeling. With the advent of increasingly powerful bisphosphonates, a normalization (at least transitory) of bone turnover can be considered in most patients. Therefore, in the context of the availability of potent bisphosphonates, the goals in the treatment of Paget disease must be readdressed [5•]. When salmon calcitonin became available in the early 1970s, a decrease in the elevated indices of pagetic bone turnover by about 50% could be obtained. This meant that in patients with mild disease, a normalization of the biochemical indices could be obtained for a while (≥1 year). The biochemical relapse recurred after variable periods of time and retreatment had to be reconsidered. For patients with very active disease, no normalization of biochemical indices could be obtained, although symptomatic relief frequently occurred. At that time, the primary reason to use antipagetic drugs was to treat the symptoms likely to respond to these agents. The indications encompassed bone pain linked to Paget disease itself (therapy was indeed much less active in osteoarthritic pain secondary to limb deformations), hypercalcemia complicating immobilization, minimizing blood losses during programmed surgery, and the rare neurologic complications attributable to spinal stenosis and vascular steal syndromes. Therapy for asymptomatic patients was reserved for patients with a very active condition, with the ostensible hope of reducing the risk of future complications by lowering the biochemical indices of bone remodeling. With the new and more potent bisphosphonates, *eg*, at first, pamidronate, and more recently alendronate and risedronate, it is possible to achieve the normalization of the biochemical indices in 60–70% of subjects with baseline indices up to four or more times the upper limit of normal [5•] for prolonged intervals (often >1 year) before abnormalities inevitably slowly recur. With retreatment, a prolonged normalization of bone indices can be obtained, with a clinically significant reduction or even halting of disease progression, although this has not yet been proven, owing to the fact that to undertake long-term placebo-controlled clinical studies to establish outcomes would be unethical. In many untreated patients as well as in patients whose abnormal bone turnover could not be fully suppressed with older treatments, ongoing increased bone turnover led to progressive disease with a clearly increased risk of a variety of complications, depending on location, extent, and activity of the disease [5•]. Conversely, the suppression of bone turnover is associated with improvement in symptoms, deposition of more normal lamellar bone, refilling as well as halting of lytic fronts, leading to a possible reduction of fracture risk [5•]. A greater suppression of turnover is seen with pamidronate, alendronate, and risedronate than with etidronate or calcitonin, both in terms of percentage decrease of indices from baseline and, more importantly, proportion of patients who achieve normal indices. Despite the absence of clear proof from randomized controlled trials that effective suppression of abnormal bone turnover in patients with Paget disease reduces the risk of future complications, the clinical evidence suggests that disease does progress in many untreated patients and that effective disease suppression would be likely to reduce future disabling problems [5•]. Therefore, it seems reasonable that the goals of therapy for Paget disease should include not only the alleviation of current symptoms but also the prevention or delay of possible future complications. When a patient has active disease, *ie*, any elevation of alkaline phosphatase above the upper limit of normal, and the presence of the condition at those skeletal sites where progression of altered bone architecture could promote future disability, treatment should be recommended, so as to reduce elevation of biochemical indices into the normal range, or, if this is not possible, as close to normal as possible. Retreatment should be considered once the bone turnover marker again exceeds the upper limit of normal (if normalized after the previous course of therapy) or increases above the prior nadir by 25% [5].

Therapy with bisphosphonates should also provoke effects on the skeleton not involved by Paget disease. In a previous study, patients with severe Paget disease treated with intravenous pamidronate showed an increase in their nonpagetic lumbar spine bone mineral density (BMD), but a decrease in forearm BMD during the 6 months after treatment [6]. It was postulated that the decrease in forearm BMD was the result of the marked secondary hyperparathyroidism after pamidronate therapy [6], a complication already observed, but at the hip, in the treatment of postmenopausal osteoporosis with high doses of intravenous pamidronate [7]. Preventive therapy with calcium and vitamin D after intravenous pamidronate treatment can be used to minimize this loss in patients with moderate or severe disease [8]. French authors have reported similar data (*ie*, a loss of – 0.84% in cortical bone mean BMD), versus a BMD gain in trabecular bone [9]. However, unexpectedly, these latter authors did not observe any significant increase in parathyroid hormone levels after pamidronate treatment, and the BMD variations were not influenced by supplemental vitamin D and calcium [9]. In the majority of patients with Paget disease and normal bone densities, such decreases in the BMD may not be clinically relevant. However, in patients whose

BMD is low before pamidronate treatment, any decrease in the bone mass of the appendicular skeleton would be undesirable and might lead to fracture [8].

Two randomized, controlled, multicenter phase III clinical studies have been conducted to determine the efficacy and safety of alendronate (40 mg/d) versus placebo for 6 months in Paget disease of bone in patients with a disease activity measured by an alkaline phosphatase activity at least twice the upper limit of normal. In the US study, etidronate was used as comparator. Alendronate decreased serum alkaline phosphatase by 79% and 73% from base line by 6 months in the US and multinational studies, respectively, whereas serum alkaline phosphatase was decreased by 44% in etidronate-treated patients and increased by 8% in placebo-treated patients [10]. In addition, 89% of alendronate-treated patients were responders, versus 30% and 0% of etidronate- and placebo-treated patients, respectively, with response being predefined as either a decrease greater than 60% from baseline or normalization of serum alkaline phosphatase. In these phase III studies, oral alendronate (40 mg/d for 6 months) was generally well tolerated. The overall safety profile of alendronate was similar to that of etidronate and placebo, and, in particular, there was no evidence of increase in the incidence of upper gastrointestinal adverse events. Oral alendronate at 40 mg/d for 6 months can be considered as a highly effective treatment for Paget disease of bone [10].

Risedronate is a pyridinyl bisphosphonate and is one of the most potent bisphosphonates in clinical development. It has been tested in an open-label, multicenter, oral dose-escalation study [11]. In this study, three different doses (10, 20, and 30 mg for 28 days) were compared in 62 patients with severe Paget disease of bone (*ie*, serum alkaline phosphatase higher than three times the upper limit of normal). The patients who received 30 mg of oral risedronate for 28 days benefited most, with a mean decrease in alkaline phosphatase excess of 72.2% (10 mg: 48%; 20 mg: 57.9%). Alkaline phosphatase normalized in 14.3% of patients in the 30-mg group (10 mg: 5%; 20 mg: 9.5%). There was a decrease of at least 50% in baseline alkaline phosphatase excess in 76% of patients receiving risedronate, 30 mg (10 mg: 50%; 20 mg: 71%); it was observed from the pagetic bone biopsies that risedronate treatment was associated with the formation of mineralized lamellar bone as opposed to abnormal woven pagetic bone. From the qualitative assessment of the biopsy specimens taken from normal bone, there was no evidence of an impairment of bone mineralization induced by risedronate. Oral risedronate was well tolerated from a gastrointestinal point of view. Two patients (one receiving 20 mg and the other receiving 30 mg of risedronate) had moderate upper gastrointestinal adverse events during the study (gastroesophageal reflux and esophagitis, respectively). Both recovered and completed the study. However, a way to improve upper gastrointestinal tolerance could be optimize esophageal transit of risedronate by using a novel cellulose film-coated tablet formulation instead of the original gelatin capsule dose form. Esophageal transit of film-coated tablets was faster (3.3 seconds) than gelatin capsules (23.8 seconds), suggesting that the former would be the appropriate formulation of risedronate [12].

Olpadronate, a new bisphosphonate characterized by the dimethylation of the amino group, conferring a potency close to that of alendronate, has been shown to be active at the dose of 200 mg/d orally for 12 days. In most of the patients, bone alkaline phosphatase normalized [13]. Various therapeutic regimens have been proposed with bisphosphonates, using differing doses of different bisphosphonates with various lengths of therapy and different outcome measurements. It is, therefore, difficult to advocate on a scientific basis a preferred regimen. The tolerance of the drug, the cost of treatment, and the severity of the condition should help the clinician in choosing the most appropriate therapy.

Spinal stenosis occurs in 10% to 20% of patients with Paget disease, half of whom have neurologic deficits. Various mechanisms of neurologic compromise have been described: a direct encroachment by the collapsed pagetic vertebrae, ossification of extradural structures, slipped intervertebral disk prolapse due to vertebral deformity, and local blood supply compromise by distortion of vessels or diversion to the highly vascular pagetic bone (vascular steal syndrome) [14,15]. Modern medical therapies for Paget disease, such as calcitonin and, more recently, one of the new bisphosphonates such as pamidronate, and tiludronate, have shown their efficacy in pagetic spinal stenosis [15]. The latter treatments, as well as alendronate and risedronate, are recommended because they do not cause the mineralization defects seen with etidronate [16,17]. Their use should obviate surgery in the vast majority of cases [15].

Fibrous dysplasia

Formerly, orthopedic surgery was the only therapy for fibrous dysplasia; it consisted of preventive means such as bony grafts, fixation, curettage, and treatment of fractures. Calcitonin has failed in the treatment of fibrous dysplasia [18]. It appears wise, however, to use antiresorptive drugs, such as potent bisphosphonates, in a condition such as fibrous dysplasia in which there is frequently an increase in bone turnover, with the presence of numerous large osteoclasts, a condition that can be compared with Paget disease of bone. Pamidronate disodium (60 mg intravenously daily for 3 days), repeated semestrially for at least 2 years, and, later, once yearly, according to the biologic and clinical response, induced in all cases a dramatic decrease (and even a disappearance) of bone pain [19,20]. There has been no resistant case in first-intention therapy, which constitutes major progress in the treatment of such a condition. Pain might recur after therapy, in about 50% of cases, but, again, after retreatment, a favorable outcome could be obtained in about 90% of cases, with a current follow-up of up to 9 years in a few patients [20]. Three patients (one adolescent aged 13 years and two adults) have shown transient mineralization defects, which fortunately completely resolved after the drug was stopped. This did not impair retreatment with pamidronate after healing of the mineralization defects [20].

Potential fetal side effects

Potential side effects of bisphosphonates in women of childbearing age should be emphasized. The molecular weight of most bisphosphonates is relatively low, probably enabling them to pass through the placenta to the embryo or fetus. In the developing fetus, bone turnover is high. Bisphosphonates administered to pregnant women (even well in advance of a planned pregnancy) could cause substantial changes in fetal skeletal growth and development, due to their long retention in bone.

In a rat study [21], alendronate administered in the human therapeutic range provoked significant effects on the fetal skeleton (increased fetal bone mass, but also decreased bone growth). Whether this can be simply translated to a human situation is not proven, but it may be advisable to use bisphosphonates in women of childbearing age with much caution. For example, bisphosphonates have been advocated as a means of preventing bone loss in young women with endometriosis, treated by luteinizing hormone–releasing hormone agonists, for improving fertility [22].

Malignant bone disease

Tumor-induced osteolysis, lytic bone disease, and humoral hypercalcemia of malignancy are all mediated by osteoclast activation. It is therefore wise to try to decrease the osteoclast activity so as to reduce skeletal complications in patients with malignant bone disease [23•]. Metastatic cancer is a major cause of morbidity for these patients and can provoke bone pain, bone fragility, fractures, and hypercalcemia. This is particularly the case in multiple myeloma and breast cancer, which have, therefore, been most studied as far as bisphosphonate action is concerned.

Multiple myeloma

Multiple myeloma is characterized by the accumulation of plasma cells in the bone marrow, with a marked increase in osteoclast activity, mediated by the local release of osteoclast-stimulating factors by cells of both tumoral and nontumoral origin. Several large randomized trials of long-term bisphosphonate use have been published. Etidronate (5 mg/kg) was not proven to be superior to placebo in a Canadian study. Oral clodronate (1.6 g/d) has been shown somewhat effective in preventing vertebral (-30%) and nonvertebral fractures (-50%), compared with placebo [24]. However, the proportion of patients requiring radiotherapy was similar between the two arms of the study, and there was no difference in time to first skeletal event or in overall survival. The results of this trial are therefore limited. Pamidronate has been studied in several trials [23•]. The results show that the adjunctive use of this bisphosphonate plus chemotherapy to prevent bone complications is superior to chemotherapy alone in patients with stage III multiple myeloma. The oral route of administration is unlikely to be effective. A 90-mg monthly intravenous dose is efficacious, but the optimal duration and dose of pamidronate are still unknown. Whether pamidronate is effective in patients who do not have overt bone disease is still unknown but is suggested by *in vitro* studies showing that the drug is able to induce apoptosis of myeloma cells [25]. However, a potential drawback could be a putative risk of tumor cell dissemination by an upregulation of the matrix metalloproteinase-2 secretion, which is involved in the metastatic process [26]. Fortunately, this potentially deleterious effect could be prevented by combining bisphosphonates with metalloproteinase inhibitors [26].

Breast cancer

Oral clodronate (1.6 g/d) is able to reduce significantly (by more than a quarter) the episodes of hypercalcemia of malignancy and the vertebral fractures but does not reduce the nonvertebral fractures nor the need for radiation therapy for bone pain. It has no significant effect on survival. Pamidronate (90 mg intravenously every 4 weeks) significantly decreased (by more than one third) the proportion of patients with metastatic breast cancer having any skeletal-related event or sustaining any pathologic fracture, by the end of 24 months of therapy, compared with placebo [27]. Unfortunately, there was no survival difference between pamidronate and placebo.

There are no published large-scale studies to support the use of bisphosphonates in metastatic prostate cancer nor in osteolytic bone metastases caused by other cancers. Bisphosphonates could be used, however, in the prevention of osteoporosis induced by chemical or hormonal castration performed for antitumor purposes. More potent bisphosphonates not only act on osteoclast-mediated bone resorption but also might affect the invasive behavior of metastatic cancer cells in bone or possess an additive or synergistic activity with cytotoxic agents. Ibandronate, a powerful aminobisphosphonate, has been shown in one study to enhance the antitumor activity of taxoids against invasion and cell adhesion to bone, which could be useful for the treatment of patients with cancer types that are known to metastasize preferentially to bone [28]. However, in another study, there was no significant effect of ibandronate on total myeloma cell burden, a study suggesting that bisphosphonates may be useful in the treatment of myeloma-associated bone destruction but that other therapies are also required to reduce tumor growth [29]. Zoledronate, a new heterocyclic imidazole bisphosphonate, is 100 to 850 times more potent than pamidronate. It is well tolerated when administered by the intravenous route. This potent compound is still currently under study in cancer trials [30].

Conclusions

Bisphosphonates have become useful antiresorptive agents over the past few years, and their availability has yielded new therapeutic approaches for bone diseases. They currently form part of established treatments for diseases such as osteoporosis, Paget disease of bone, humoral hypercalcemia of malignancy, multiple myeloma, and bone metastases. As new, more potent bisphosphonates are developed, there is hope that they could be of help by having an antitumor effect per se, by preventing erosions in rheumatoid arthritis, and by preventing loosening of joint prostheses. These compounds possess potential for use in a large spectrum of bone diseases, and this should be demonstrated, hopefully, in the near future.

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